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TAR DNA-binding protein-43 in amyotrophic lateral sclerosis, frontotemporal lobar degeneration, and Alzheimer disease

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Issue overview

The current issue of *Acta Neuropathologica* is devoted to transactive response DNA-binding protein-43 (TAR DNA-binding protein-43, TARDBP-43, TARDBP, or TDP-43)-related proteinopathies and contains nine papers concerning new developments in this field. There are four papers analyzing various aspects of TDP-43 in amyotrophic lateral sclerosis (ALS), one paper staging TDP-43 pathology in Alzheimer's disease (AD), two papers describing the experience at two different institutions with TDP-43 negative frontotemporal lobar degeneration with ubiquitinated inclusions (FTLD-U), a paper detailing the ultrastructural features of TDP-43 positive inclusions in FTLD-U, ALS, and other neurodegenerative diseases, and a paper describing analysis of TDP-43 in plasma by ELISA.

TDP-43 in ALS, FTLD-MND, and FTLD-U: background

Molecular and pathologic progress in FTLD-U over the past 2 years has been absolutely stunning. Given the fact that FTLD-U is the single most common pathologic entity among the FTLD group [1,2], and that the FTLD group can be separated into the two approximately equal broad categories of tauopathies and ubiquitinopathies on the basis of the presence or absence of tau-positive or tau-negative, ubiquitin-positive inclusions [3,4], the significance of this progress cannot be overestimated. Less than 2 years ago, the gene responsible for chromosome 17-linked FTLD-U had not been identified as *PROGRANULIN* (*PGRN*) and the major protein component of the ubiquitinated inclusions had yet to be identified as TDP-43. But in August 2006, two papers revealed that *PGRN* mutations are responsible for Chr17-linked FTLD-U [5,6], and 2 months later, two papers identified TDP-43 as the major protein component of inclusions in both FTLD-U and ALS [7,8]. Roles for *PGRN* and TDP-43 in the brain had previously been unknown. A literature search for articles about *PGRN* prior to August 2006 would have produced papers related to malignancy and inflammation and a search for TDP-43 prior to October 2006 would have resulted in a small handful of papers related to cystic fibrosis and human immunodeficiency virus. Today's search, sure to increase by the time this article appears in print, reveals approximately 90 articles concerning *PGRN* and FTLD and approximately 70 about TDP-43 and FTLD. With nine papers pertaining to TDP-43 in this issue of *Acta Neuropathologica* alone, it is apparent how far the field has progressed.

In the early 1990s, ubiquitin-positive inclusions were described in extra-motor cortex in ALS [9] and in ALS with dementia [10]; these were later described in frontotemporal dementia without ALS [11], now called FTLD-U. It eventually became evident that the close clinical

and pathologic relationship between ALS, or motor neuron disease (MND), and FTLN suggested that ALS, ALS with dementia or FTLN-MND, and FTLN-U without MND represented a clinicopathologic spectrum [12]. Likewise, the fact that most, if not all, cases of dementia lacking distinctive histology (DLN) [13] were proved to be FTLN-U [1,2,14,15] meant that FTLN-U was the most common underlying pathology in FTLN. The discovery that TDP-43 was the major component of the ubiquitinated inclusions in both FTLN-U and most cases of ALS linked the two at the molecular level [7,8,16-22].

“Maturation” of TDP-43 positive inclusions in ALS

TDP-43 is a 43-kD highly conserved and widely expressed normal nuclear protein encoded by the *TARDBP* gene on chromosome 1. When abnormal TDP-43 aggregates and forms cytoplasmic inclusions, normal nuclear positivity is lost. Granular cytoplasmic TDP-43 positive inclusions in neurons with absent nuclear TDP-43 labeling have been interpreted as “pre-inclusions” [16,23,24]. However, the paper by Mori et al. [25] in this issue suggesting that TDP-positive round inclusions develop from small dense granules whereas skein-like inclusions (SLIs) develop from “linear wisps” and that diffuse punctuate cytoplasmic staining is present in normal controls as well as in ALS cases, casts doubt upon that hypothesis. In addition, this report shows that SLIs are ultrastructurally granulofilamentous, similar to a recent report by Hasegawa et al. [26] and in contrast to another report showing that FTLN-U cytoplasmic inclusions (CIs) are predominantly granular [24], suggesting either that SLIs are ultrastructurally dissimilar from FTLN-U CIs or that the ultrastructural characteristics of these inclusions are yet to be completely delineated. Additionally, the paper by Lin and Dickson [27] in the current issue also shows that TDP-43 positive inclusions in both FTLN-U and ALS are predominantly granulofilamentous and occasionally filamentous only but not granular only. This paper also shows similar inclusions occasionally associated with neurofibrillary tangles in AD, Pick bodies in Pick disease, and alpha-synuclein filaments in Lewy bodies and Lewy neurites in Lewy body disease, which may explain the occasional immunolabeling of these inclusions with TDP-43.

TDP-43 positive inclusions in ALS—protective or toxic?

The functions of TDP-43 are diverse and incompletely understood. However, TDP-43 appears to bind to DNA, RNA, and protein. In FTLN-U, TDP-43 is abnormally phosphorylated, ubiquitinated, and enzymatically hydrolyzed in a manner that produces two abnormal C-terminal products of 23 and 27 kD [7]. What remains unclear is what that molecular evidence reveals about the pathophysiology of FTLN-U and ALS. Some insight was gained from papers showing that lower motor neurons in ALS with Golgi apparatus fragmentation had TDP-43 positive cytoplasmic inclusions, suggesting that abnormalities in TDP-43 are associated with dysfunction of neuronal secretory pathways [28], that TDP-43 binds to and possibly stabilizes human low molecular weight neurofilament mRNA within the nucleus and possibly during nuclear-cytoplasmic transport [29], and that TDP-43 does not label the ubiquitin-positive lower motor neuron inclusions in familial ALS cases with SOD1 mutations [30,31]. Because mutants of human and *Drosophila* *TDP-43* that lack the C-terminal domain are unable to affect splicing [32], and because the C-terminal fragments are aggregated in the urea soluble fraction of human brain homogenates, it seemed likely that TDP-43 aggregates result in loss of function rather than a toxic gain of function. The paper by Pamphlett and Jew [33] in this issue casts doubt on that hypothesis, presenting evidence that TDP-43 positive inclusions do not protect motor neurons from neuronophagia in ALS. Supporting the concept that TDP-43 aggregates may be toxic is an exciting report of a recently developed yeast TDP-43 proteinopathy model that remarkably recapitulates many of the features of human TDP-43 proteinopathy—including nuclear localization and cytoplasmic aggregation, with growth inhibition resulting from aggregation of TDP-43 [34].

TDP-43 processing in neurons and glia in ALS and FTL-D-MND

Additional data suggest that TDP-43 also resides in the dendritic processing body of somatodendrites, in the form of RNA granules that colocalize with the postsynaptic protein PSD95, where it acts as a translational repressor and thus likely helps regulate neuronal plasticity [35]. It is noteworthy that Lin and Dickson [27] detected TDP-43 positive immunogold-labeled filaments in neuronal processes that appear to be dendrites. There is evidence that there are region-specific pathways of TDP-43 processing, in that TDP-43 positive inclusions in neocortex and hippocampus are enriched in C-terminal fragments while spinal cord inclusions appear to be composed of full-length TDP-43 [36]. Widespread neuronal and glial TDP-43 pathology is found in ALS, and interestingly, neuronal TDP-43 positive inclusions are almost all ubiquitinated while white matter glial inclusions are generally not [37]. The studies by Nishihira et al. [38] and Hiji et al. [39] in this issue look in further detail into the distribution and immunohistochemical labeling pattern of TDP-43 positive inclusions in FTL-D-MND and ALS. Nishihira et al. [38] show two types of TDP-43 immunohistochemical patterns—type (1) widespread cortical and subcortical inclusions, and type (2) inclusions predominantly in motor regions, and show a significant correlation of the type 1 pattern with dementia (FTL-D-MND) that is not affected by long-term artificial respiratory support. Likewise, Hiji et al. show that subcortical white matter inclusions are found diffusely in FTL-D-MND, while white matter inclusions in ALS appear to be restricted to motor regions. As previously reported, they also found that while these glial inclusions label with antibodies to both TDP-43 and p62, they are not ubiquitinated. The Hiji et al. [39] study may explain the absence of ubiquitination of white matter inclusions: they show that biochemically, TDP-43 in white matter is different from TDP-43 in gray matter, in that it is apparently not cleaved, but formed of full-length TDP-43, suggesting that ubiquitination of TDP-43 occurs only after cleavage, and also supporting the hypothesis above of region-specific processing pathways. This differs, however, from another report that TDP-43 is hyperphosphorylated and truncated in white matter just as it is in gray matter [40]. On the other hand, another report suggests something completely different using “deconvolution imaging” with TDP-43 and ubiquitin antibodies: that TDP-43 is not even the major ubiquitinated protein in ALS [41]. Whether TDP-43 in white matter is cleaved or full length and whether the major ubiquitinated protein in ALS is truly TDP-43 need further study.

TDP-43 in other neurodegenerative disorders

Likewise, there is conflicting information in the literature with regard to whether TDP-43 is present in other neurodegenerative disorders. One paper reported TDP-43 positivity in most FTL-D-U and FTL-D-MND cases, including all familial cases with mutations in *PGRN*, valosin-containing protein *VCP*, and linkage to chromosome 9p without *VCP* mutations, but no TDP-43 positivity in cases of FTL-D-U with mutations in *CHMP2B*, or in cases of AD, diffuse Lewy body disease (DLBD), a variety of tauopathies (Pick disease, corticobasal degeneration, progressive supranuclear palsy, and argyrophilic grain disease [24]. Others have also found no TDP-43 positive inclusions in pure DLBD [42]. However, still others have reported TDP-43 positive inclusions in up to 30% of AD, in combined ADDLBD, in pure DLBD, in the dentate fascia in 70% of hippocampal sclerosis cases [42–45], in some cases of Pick disease [8,46], in AD and CBD but not in other tauopathies [47], and in most cases of Guamanian ALS–parkinsonism–dementia complex [48,49]. Interestingly, in an immunohistochemical analysis of TDP-43 in five cases of PPA with AD pathology, which might be expected to have concomitant TDP-43 positive inclusions, *none* did; all had AD pathology only [50]. On the other hand, one of the papers in the current issue [51] documents the distribution of TDP-43 pathology in 29 cases of AD previously shown to have TDP-43 pathology [43]. All cases were Braak and Braak stage V or VI. Three stages of TDP-43 pathology were identified: (1) amygdala only (six cases), (2) amygdala and hippocampus only (seven cases), and (3)

amygdala, hippocampus, and neocortex. Authors suggest that these stages are comparable to Braak and Braak tangle or Lewy body stages. No cases had CIs in the hypoglossal nucleus, making the possibility of combined AD and ALS unlikely. Interestingly, the cases with mixed pathology had more severe clinical phenotypes. The authors recommend that in evaluating cases of AD for TDP-43 pathology, multiple brain regions need to be examined. Clearly, however, the literature contains conflicting reports and additional work remains to be done.

TDP-43 negative FTL-D-U

Additionally, there appears to be a subset of FTL-D-U cases that are TDP-43 negative [24,52] that some are calling “atypical FTL-D-U.” In the current issue, there are two additional papers detailing the clinical and pathologic findings in cases of “atypical FTL-D-U” from two separate centers: (1) Mayo Jacksonville [53] and (2) Ludwig-Maximilians University in Munich [54]. In the Mayo series, 3 of 44 FTL-D-U cases were positive for ubiquitin and p62 but negative for TDP-43. Two patients presented with behavioral variant FTL-D at young ages, one with a positive family history; one presented with corticobasal syndrome. There were no neuronal intranuclear inclusions (NIIs). EM showed granulofilamentous inclusions similar to those demonstrated in SLIs in ALS [25] and in TDP-43 immuno-labeled inclusions in FTL-D-U and ALS [27], again in contrast to the granular inclusions previously reported in FTL-D-U [24]. In the Munich series, 9 of 44 FTL-D-U cases were positive for ubiquitin and p62 and negative for TDP-43. These were all sporadic with early onset. All had hippocampal sclerosis and all had unusual curved or twisted NIIs that were negative for p62. Biochemical analysis showed that all cases had normal full-length TDP-43. So while there are several reports on “atypical FTL-D-U,” there are different findings from different groups. Those working in this field, however, know that TDP-43 immunohistochemistry is finicky, that different techniques produce different results, and that this must be considered when evaluating conclusions.

TDP-43 mutations

Some of the most exciting recent news is that *TDP-43* mutations have been reported in cases of familial and sporadic ALS [55-58]. These cases more closely parallel the situation in most inherited neurodegenerative disorders in which mutations are found in genes coding for the aggregating abnormal protein, and give additional credibility to reports that the identity of the major abnormal protein, at least in ALS, is TDP-43. Although to date there have been no mutations reported in FTL-D [59,60], this news cannot be far behind.

Blood test for FTL-D-U?

The remaining paper from this issue to be discussed, by Foulds et al. [61] is potentially the most exciting. This group analyzed TDP-43 in plasma using ELISA. Results showed elevated levels in 46% of clinically diagnosed FTL-D, the approximate percentage of FTL-D cases that have FTL-D-U, and 22% of clinically diagnosed probable AD, the approximate percentage of cases of AD that have TDP-43 positive inclusions, compared to 8% of control subjects. The same results now remain to be demonstrated in antemortem plasma samples from pathologically proven FTL-D-U. If this were to produce similar results, FTL-D-U would be the first neurodegenerative disease for which there is a blood test. Identification of patients likely to respond to eventual targeted therapies is crucial and this may be the first step toward such a test.

Conclusions

These are exciting times in FTL-D research, with progress beginning to catch up to that reached in AD 15 years ago. Hypotheses can now be developed and tested and the pace is frantic. The

authors of the papers in this issue of *Acta Neuropathologica* generously add to the body of knowledge about TDP-43 and its role in FTLT.

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